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EXAMINER

WOODWARD, CHERIE MICHELLE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Formal Matters

1. Applicant's Response filed 3/5/2008 is acknowledged and entered. Claims 1-36 are pending. Claims 12-22 and 29-36 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-11 and 23-28 are under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 3/5/2008 has been considered by the examiner. A signed copy is attached hereto.

Response to Arguments

Claim Objections Withdrawn

3. The objection over claim 1 because of the misspelling of the word "hormone" is withdrawn in light of Applicant's amendments.

Claim Rejections Maintained

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-11 and 23-28 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al., US Patent 4,962,212 (10 April 1990) and Schweden et al., US Patent 5,672,487 (30 September 1997), as evidenced by Hollenberg et al., (Curr Opin Biotechnol. 1997 Oct;8(5):554-60, Abstract Only), and Weidemann et al., (FEBS Lett. 1989. Oct 23; 257(1):31-4), for the reasons of record and the reasons set forth herein.

Applicant argues that there is no justification or suggestion to combine the references or to combine them in the manner proposed (Remarks, p. 1 of 7, fifth paragraph). Applicant cites *In re Mills* in support of this argument (Remarks, page 2 of 7, third paragraph). Applicant also argues that recombinant protein expression in a foreign host is highly unpredictable (Remarks, p. 2 of 7, fourth paragraph). In support of this argument, Applicant cites the Laforet et al., Kjaerulff, and Murasugi et al., references (Remarks, page 2 of 7, fourth paragraph to page 4, first paragraph). Applicant argues that the *Schwanniomyces occidentalis* glucoamylase and *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequences are very different from Mf-alpha signal sequences in terms of their origin and structure (Remarks, page 4 of 7, second full paragraph). Applicant argues that it would not be obvious to one of ordinary skill in the art that high expression of insulin precursors would be possible using *Schwanniomyces occidentalis* glucoamylase and *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequences in view of the prior art (Remarks, page 4 of 7, second full paragraph). Applicant argues that the '487 patent does not mention insulin in the specification and that the term "protein" is not exemplified [sic] to include specific disclosures (Remarks, page 4 of 7, last paragraph). Applicant argues that the hirudin protein taught by the '487 patent are structurally and functionally different (Remarks, page 4 of 7, last paragraph). Applicant argues that there is no implicit or explicit teaching, suggestion, or motivation in either the '212 or the '487 patent regarding the use of *Schwanniomyces occidentalis* glycoamylase and *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequences in place of Mf-alpha signal sequences which would lead a person of ordinary skill in the art to use the sequences

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to prepare insulin at high yields (Remarks, p. 4 of 7, last paragraph to page 5 of 7, first paragraph). Applicant argues that the references themselves or some other prior art must suggested that they be combined (citing *In re Sernaker* CAFC 1983), *Orthopedic Equipment Co., v United States* (CAFC 1983) (Remarks, page 5 of 7, second paragraph). Applicant also cites *Uniroyal Inc. v. Rudkin-Wiley Corp* (CAFC 1988) and *Ex parte Levengood* (BPAI 1993) in support of this argument (Remarks, p. 5 of 7, last two paragraphs). Applicant also argues hindsight reasoning on page 6 of 7, second paragraph. Applicant argues that no reasoning is given in the Office Action to support the combination of the references (Remarks, page 6 of 7, third paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

The construct of the instant invention is a composition comprising a yeast promoter followed by a signal peptide from the recited species of *Schwanniomyces occidentalis* glucoamylase signal peptide sequence or *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequence followed by an insulin pre-pro-peptide. The examiner previously discussed the '212 patent, which teaches DNA constructs comprising human insulin precursors expressed in yeasts, meeting the limitations of instant claims 1, 4-11, 23, and 25. The examiner also stated that the '212 patent does not teach a yeast DNA construct with signal sequences from the species of *Schwanniomyces occidentalis* glucoamylase or the *Carcinus maenas* crustacean hyperglycemic hormone. The '487 patent was cited because it teaches construction of vectors for the secretory expression of recombinant proteins from the yeast *Hansenula polymorpha* including yeasts with the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* and the leader sequence from the hyperglycemic hormone of the shore crab (*Carnius maenas*).

With regard to Applicant's argument that there is no justification or suggestion to combine the references or to combine them in the manner proposed (Remarks, p. 1 of 7, fifth paragraph), the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the '487 patent itself provides the rationale and motivation to use a construct comprising vectors for the use of large (i.e. commercial-scale) secretory expression of recombinant proteins in *Hansenula polymorpha* yeasts using signal sequences from *Schwanniomyces occidentalis* or the signal sequence of the crustacean hyperglycemic hormone from *Carnius maenas*. The '487 patent teaches that the use of these signal sequences in these yeasts is known,

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tested, proven, successful, and predictable. Moreover, the '487 patent teaches that any generic protein may be used in the yeast expression system, "in particular proteins which are foreign to yeasts, ie. heterologous, in the yeast *Hansenula*, which ensures efficient secretion and correct processing for a large number of proteins" (column 1, lines 36-41). The '212 patent teaches production of the insulin pre-pro peptides with the addition of selective cleavage sites adjacent to the N-terminal of the pre-pro-insulin peptide sequences that are produced in yeasts that would enable subsequent splitting off of the additional protein either by the microorganism itself or by later enzymatic or chemical cleavage. Thus, the '487 provides the rationale and motivation to use *Hansenula polymorpha* yeasts to produce recombinant proteins in using signal sequences from *Schwanniomyces occidentalis* or the signal sequence of the crustacean hyperglycemic hormone from *Carcinus maenas* and the '212 patent demonstrates that the commercially important, well known, and well characterized insulin pre-pro-peptide can have cleavage sites added to aid in recombinant protein expression without adversely affecting the functional properties of the peptide.

Applicant's argument that it would not be obvious to one of ordinary skill in the art that high expression of insulin precursors would be possible using *Schwanniomyces occidentalis* glucoamylase and *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequences in view of the prior art (Remarks, page 4 of 7, second full paragraph), is not supported by the findings in the '487 patent that any recombinant protein can be expressed at high levels using *Hansenula* yeasts and the *Schwanniomyces occidentalis* glucoamylase and *Carcinus maenas* crustacean hyperglycemic hormone signal peptide sequences (see above). The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Insofar as Applicant argues against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument that recombinant protein expression in a foreign host is highly unpredictable (Remarks, p. 2 of 7, fourth paragraph), the prior art itself provides the level of predictability in the instant case. The '487 patent teaches construction of vectors for the secretory expression of recombinant proteins from the yeast *Hansenula polymorpha*. The '487 patent also teaches the use of the glucoamylase leader sequence (GAM1) from *Schwanniomyces occidentalis* as well as the

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shore crab signal sequence which was found to be identical to the signal sequence of the crustacean hyperglycemic hormone (CHH) from *Carnius maenas*. The teaching of vectors for the use of secretory expression of recombinant proteins in *Hansenula polymorpha* yeasts using signal sequences from *Schwanniomyces occidentalis* or the signal sequence of the crustacean hyperglycemic hormone from *Carnius maenas* is old and well known in the art and would have been predictable to one of ordinary skill in the art at the time the instant invention was made. The addition of the insulin pre-pro-peptide was merely a commercially driven design choice. Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art, as in the instant case.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

NO CLAIM IS ALLOWED.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CMW/

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/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646